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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,217	02/21/2002	Gregory R. Mundy	10274-063001 / A061CIP2 U	5114

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
01/30/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/086,217	MUNDY ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *86-98 and 100-102* is/are pending in the application.

4a) Of the above claim(s) *90* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *86-89, 91-98 and 100-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/31/07 has been entered.

2. Claims 86-98 and 100-102 are pending.

3. Claim 90 stands withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to a nonelected invention.

4. Claims 86-89, 91-98 and 100-102 are under consideration in the instant application as they read on a method of treating multiple myeloma with a composition comprising an anti-VLA-4 antibody and the species of chemotherapeutic agent melphalan.

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 86-89, 91-98 and 100-102 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,692,742 (listed previous on PTO-892) in view of Lokhorst et al (Blood 84:2269-2277, 1994) and Masellis-Smith et al (IDS Ref No. A1).

The US `742 patent teaches teach and claims a method for treating multiple myeloma patients comprising administering anti-IL-6 antibodies (a reshaped human PM-1 antibody) with melphalan to a subject in need of such treatment (see patented claim 1in particular), wherein the

reshaped human PM-1 antibody is the antibody hPM-1(see patented claim 2 in particular). Anti-IL-6 receptor antibodies act via binding to IL-6 receptor, block the binding of IL-6 to IL-6 receptor, and thereby inhibit signal transmission of IL-6, and therefore are antibodies which inhibit the biological activity of IL-6. The `742 patent further teaches that the effective dosage of anti-IL-6 receptor antibody is chosen from the range of 0.001 mg to 1000 mg per kg of body weight per day. Preferably, the dosage is selected from the range of 0.01 to 50 mg per body weight (see col., 15, line 24-28 in particular). The `742 patent teaches that monoclonal antibodies (col., 8, line 2), chimeric antibody and humanized antibody can be used for the purpose of lowering xenogenic antigenicity against humans (see co., 9, lines 1-6 in particular). Further, the `742 patent teaches that human antibody having the activity of binding to and neutralizing IL-6 receptor (col., 7, lines 33-41 in particular). In addition, the `742 patent teaches that fragments of antibody such as Fab, F(ab')2, Fv or single-chain Fv (scFv) (see col., 10, lines 33-35 in particular). Furthermore, the ` 742 patent teaches compositions comprising a nitrogen mustard anticancer agent and anti-IL-6 receptor antibody (see col., 15, lines 13-15 in particular). Finally, the `742 patent has found that the combination of a nitrogen mustard anticancer agent (such as melphalan), a conventionally known anticancer agent, and anti-IL-6 receptor antibody has a synergistic effect, i.e. it is more effective than the sole use of the nitrogen mustard anticancer agent or the sole use of anti-IL-6 receptor antibody for treatment of myeloma (see col. 1, line 66 to col., 2, line 6, Fig. 9 and Examples 1 and 2 in particular).

The reference teaching differs from the claimed invention by not expressly disclosing to employ an antibody anti-VLA-4 antibody or antigen binding fragment thereof in claims 86, 100 and 101.

Lokhorst *et al* teach monoclonal antibodies directed to the α4-integrin (VLA-4) that inhibit binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma. Furthermore, the antibodies to VLA-4 inhibited the induced IL-6 secretion. Furthermore, Lokhorst *et al* teach that the intimate cell-cell contact is a prerequisite for IL-6 induction and the physical separation of plasma cells and LTBMC by mechanical means such as monoclonal antibodies to VLA-4 which is involved in the adhesion process, inhibit the induction of IL-6 production by LTBMC (entire document and abstract page 2269, and page 2276, left column 2nd paragraph in particular).

Masellis-Smith *et al* teach function-blocking monoclonal antibodies such as mAbs against very late antigen 4 that inhibit the CD19+ multiple myelom blood B cell interaction with BM fibroblasts. Furthermore, Masellis-Smith *et al* teach that the alpha4beta7 ligand is mediated MM blood B cell adhesion (see the entire document and abstract page 930 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-IL-6 receptor antibody taught by the `742 patent with the antibody that specifically binds VLA-4 antibody taught by Lokhorst *et al.*, and Masellis-Smith *et al* in a method of treating multiple myeloma (MM) taught by the `742 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to to do so because antibodies against alpha4 integrin inhibit cell-cell contact which is a prerequisite for IL-6 induction as taught by Lokhorst *et al* and because antibodies against alpha4 integrin inhibit the adhesion of alpha4beta7 integrin of B cells from MM patients with its ligand on the bone marrow (BM) fibroblast and hence prevent extravasation into the BM.

Claim 97 is included because the referenced anti-VLA-4 antibodies are B epitope because anti-alpha4 antibody is an antibody which can bind VLA-4 at a site involved in ligand recognition and block VCAM-1 binding. Thus the referenced anti-VLA-4 antibody belongs by definition to the B epitope-specific group. Therefore, being B-epitope-specific is considered an inherent property of the referenced antibody.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 10/31/07, have been fully considered, but have not been found convincing.

Applicants submit that they have presented evidence showing that anti-VLA-4 antibodies and anti-IL-6 receptor antibodies are not interchangeable for treatment of MM. For example, Applicants presented evidence that anti-IL6 receptor antibodies and anti-VLA-4 antibodies will disrupt different biological pathways. In the Declaration submitted with the Reply to Office Action on September 11, 2006 ("the Mundy Declaration"), Dr. Mundy, an inventor named on the pending application, explained that an anti-IL-6 receptor antibody interacts with at least two different classes of ligands, one class being the gp 130 ligands and the other class being the gp80 ligands. An anti-IL6 receptor antibody will therefore disrupt a multitude of pathways involving these ligands. See the Mundy Declaration at paragraph 7. Dr. Mundy also explained that anti-VLA-4 antibodies are believed to work through mechanisms that are independent of IL-6. See the Mundy Declaration at paragraph 5. Anti-VLA-4 antibodies kill myeloma cells by blocking direct interactions between myeloma cells and normal host cells in the bone marrow. When the myeloma cells cannot attach to the normal host cells, the myeloma cells die. There may be a concomitant decrease in IL-6 levels following administration of anti-VLA-4 (as suggested by the in vitro findings of Lokhorst), but this would be a byproduct and not the direct cause of myeloma cell death, nor the reason why the myeloma cells die. Applicants accordingly disagree with Examiner's conclusory statement at page 3 of the Office Action that "by inhibiting the upstream VLA-4 molecule using antibodies, the skilled in the art would be targeting the same pathway of IL-6 interaction because VLA-4 is upstream of the IL-6 production.

However, bbviousness challenge is not limited to the problem the patentee was trying to solve or to only those prior art elements designed to solve the same problem. The combination of "familiar elements" according to "known methods" is likely to be obvious when it does no more than yield "predictable results". The rational of combining the references flows logically from the `742 patent teachings methods of treating MM with anti-IL-6 receptor antibodies and melphalan, antibodies which inhibit the biological activity of IL-6, to the Lokhorst et al teachings that monoclonal antibodies directed to the α4-integrin (VLA-4) that inhibit binding of purified myeloma cells to long term bone marrow cultures (LTBMC) from patients with multiple myeloma. Furthermore, the antibodies to VLA-4 inhibited the induced IL-6 secretion. Given that antibodies against alpha4 integrin inhibit cell-cell contact which is a prerequisite for IL-6 induction as taught by Lokhorst et al the ordinary skilled in the art would be motivated to substitute the anti-IL6 receptor antibody taught by the `742 patent with the anti-VLA-4 antibodies taught by Lokhorst et al to yield predictable reduction of IL-6, whether directly or as byproduct, i.e., irrespective of the mechanism of actions. Further, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed the mechanism by which a particular anti-VLA-4 antibodies and a melphalan alleviates symptoms of MM does not appear to distinguish the prior art teaching the same methods to achieve the same end result.

Applicants further submit that the Mundy Declaration also noted that the prior art reference Bataille et al. (Blood 86:685-691, 1995; cited in the IDS submitted June 21, 2002) taught that anti-IL-6 antibodies were not effective at treating MM. Bataille et al. reported that patients with advanced MM did not achieve remission or improved outcome following treatment with murine anti-IL-6 monoclonal antibodies. See the Mundy Declaration at paragraph 4. The '472 patent also disclosed that IL-6 receptor antibodies alone were ineffective in the absence of chemotherapeutic agent. See the '472 patent at col. 20, lines 23-35; and col. 22, lines 13-20 and 49-53, and Table 2. This is in contrast to Applicants' findings, which included evidence that anti-VLA-4 antibodies alone decreased tumor burden in vivo in a mouse model of myeloma bone disease (see Specification at, e.g., page 66, lines 14-26, and the published results in Moil et al. Blood 104:2149-2154, 2004, cited in the IDS submitted September 11, 2006). Thus, even if anti-VLA-4 antibodies inhibit IL-6 (which Examiner reads Lokhorst to suggest), one would not expect IL-6 inhibitory agents to be interchangeable with anti-VLA-4 inhibitory agents to effectively treat MM, whether alone or in combination with any other agent.

However, the Examiner's position is that both the `742 patent and the claimed invention are directed to combination therapy in treating MM. Further, the `742 patent claims and teach the use of anti-IL-6 receptor antibodies with melphalan to treat MM. The claims are presumed enabled. Regarding Bataille et al, the examiner notes that while the '742 patent is presumed enabled for both the advance MM as well as acute-phase MM, the instant application claims do not exclude any phase of MM in the method of treating MM. The instant claims read on all types of MM. Further, the claims are directed to methods of treating, not methods of curing.

Accordingly, any measurable level of improvement in either Bataille et al or `742 patent is considered a treatment of MM.

Applicants submit that in the May 16th Reply, they presented evidence of surprising results following treatment of MM with a combination therapy including anti-VLA-4 antibodies and melphalan. In the May 16th Reply, Applicants' noted the synergistic results described in the specification at page 72, lines 6-18, and Figure 8, which describes a significant decrease in serum IgG2 levels (an indicator of decreased tumor burden) in mice treated with a combination of anti-VLA-4 antibodies and melphalan. This result was surprising in view of the observation that no significant decrease was observed following treatment with either agent alone in this particular experimental model.

However, the same surprising "synergistic results" are taught by the `742 patent. The `742 patent teaches that the combination of a nitrogen mustard anticancer agent (such as melphalan), a conventionally known anticancer agent, and anti-IL-6 receptor antibody has a synergistic effect, i.e. it is more effective than the sole use of the nitrogen mustard anticancer agent or the sole use of anti-IL-6 receptor antibody for treatment of myeloma (see col. 1, line 66 to col., 2, line 6, Fig. 9 and Examples 1 and 2 in particular).

Applicants point that the U.S. Patent and Trademark Office (USPTO) now relies on KSR International Co. v. Teleflex Inc., 550 U.S. ---, 127 S.Ct. 1727 (2007), for guidance in applying the standard under 35 USC § 103. The facts in KSR concerned a small number of single references, applied in a straight-forward way to a highly predictable technology. That situation stands in stark contrast to the present matter. The present rejection relies on complicated subject matter, and three references that were applied in a complex, highly unpredictable technology. This is just the type of situation that the Supreme Court in KSR and its progeny, e.g., *Takeda Chemical Industries, Ltd. v. Alphapharm PW.*, Ltd., 492 F.3d 1350 USPQ2d 1169 (Fed. Cir. 2007), cautioned against. See, e.g., KSR at 1740.

However, since the combined reference teachings suggested the invention method with predictable results (decrease in IL-6 production in combination of chemotherapy would result in treatment of MM). Applicants had a reasonable expectation of success. Applicants merely used routine methods to prove what was already believed to be the case.

Applicants maintain that the evidence as a whole indicates that one of ordinary skill in the art would not be motivated to substitute the anti-IL-6 receptor antibodies of the '472 patent with anti-VLA-4 antibodies for the treatment of MM, even in view of the disclosures of Lokhorst et al. and Masellis-Smith et al.

The Examiner's position is that the skilled in the art would be motivated to do the substitution because anti-VLA-4 antibodies would decrease the production of IL-6 mediated by the cell surface VLA-4 ligation. IL-6 is considered the most important growth factor for malignant cells in MM (see Lokhorst, introduction).

Applicants assert that none of the cited references, alone or in combination, explicitly or implicitly teach or suggest treatment of MM by administering an anti-alpha4 integrin antibody, such as an anti-VLA4 antibody (or an antigen binding fragment thereof), in combination with a chemotherapeutic agent. There is also no explicit or implicit suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the teachings of the '472 patent, Masellis-Smith and Lokhorst to arrive at the claimed methods.

However, the rationale to support a conclusion that the claims would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods with no change in their respective functions and the combination would have yielded nothing more than predictable results of treating MM. The Examiner's position is that the combined reference teachings provide teachings, suggestion and motivation to treat MM with anti-VLA-4 antibodies and chemotherapeutic agent. The substitution of anti-VLA-4 antibodies for the anti-IL-6 receptor antibodies in a combinational therapy would have yielded predictable results of treating MM.

Applicant submits that without an explicit reason to alter the teachings of the prior art to arrive at the presently claimed methods, the obviousness rejection fails.

Again the reason to substitute is to decrease the production of IL-6 (directly or indirectly) mediated by the cell surface VLA-4 ligation, wherein the IL-6 enhances MM cell growth and proliferation. An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. V. Teleflex Inc.,* 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Applicants argue that while Lokhorst teaches that anti-VLA-4 antibodies inhibited binding of purified myeloma cells to LTBMC cells in vitro, and inhibition of this cell-cell contact inhibited IL-6 secretion by the LTBMC cells, Applicants have presented other evidence that counters the teachings of Lokhorst at least insofar as Lokhorst may be relevant to treatments of multiple myeloma. For example, Bataille et al. reported that patients with advanced MM did not achieve remission or improved outcome following treatment with murine anti-IL-6 monoclonal antibodies, and the '472 patent reported that anti-IL-6 receptor antibodies alone were not effective for treatment of MM in a mouse model (see above). Thus, in view of the evidence as a whole, one of ordinary skill in the art would not have found a reason in the '742 patent to substitute the anti-IL-6 receptor antibodies of the '742 patent with an anti-VLA-4 antibody in combination with a chemotherapeutic agent for the treatment of MM, even in view of one or both of Lokhorst et al. and Masellis-Smith et al.

The Examiner notes that the scope of the claimed invention requires the combination therapy of both anti-VLA-4 antibody and chemotherapy agent not a single drug administration as argued by Bataille et al report. However, the '742 patent teaches and claims the combination therapy of both anti-IL-6 receptor antibody and a chemotherapeutic agent in treatment of MM. Given that Lokhorst teaches that anti-VLA-4 antibodies inhibited binding of purified myeloma cells to LTBMC cells in vitro, and inhibition of this cell-cell contact inhibited IL-6 secretion by the LTBMC cells, the skilled in the art at the time of Applicant's invention would have been motivated to substitute the anti-IL-6 receptor antibody with the anti-VLA-4 antibody in combination with a chemotherapeutic agent in a method of treating MM. The antibody substitution in the combination therapy would have yielded nothing more than predictable result of treating MM.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

January 16, 2008

Maher Haddad

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